MINUTES

Roberts/RiboGene Experts Meeting for the Metoclopramide Nasal Spray Phase III Studies

ATTENDEES:

Michael Petrone, MD	VP, Medical Affairs, Roberts Pharmaceutical Corporation
Glenn Thompson	Roberts Pharmaceutical Canada, Inc.
Alvin Howard	VP, Regulatory Affairs, Roberts Pharmaceutical Corporation
Laura Lehman, PhD	VP, Research, RiboGene
Gerda Vlasitz-Kocks	General Manager, Verum Staticon/VRG
David Young, PhD, PharmD	President and CEO, GloboMax LLC
Carol Trapnell, MD	Director, Medical Affairs, GloboMax LLC
Ruth Oliver, PhD	Senior Scientist, Team Leader, GloboMax LLC
Judith Chiostri, MS	Project Coordinator, GloboMax LLC
Patricia Corey-Lisle, MSN	Senior Clinical Scientist, GloboMax LLC
Eugene Heyman, PhD	Director, Biostatistics & Data Management, GloboMax LLC
Robert Ratner, MD	Expert Consultant
Janice Gilden, MD	Expert Consultant
Richard McCallum, MD	Expert Consultant
Robin Rothstein, MD	Expert Consultant

10:10 am Start of Discussion at: GloboMax LLC, 7250 Parkway Drive, Suite 430, Hanover, MD 21076

Welcome and Introductions — **M. Petrone, All**

Introduction of Program — **C. Trapnell**

- **Two Protocols and Overview of Development Program**

Role of Verum/Staticon/VRG — **Gerda Vlasitz-Kocks, All**

- **Clinical site start-up, monitoring and investigator selection/meeting**
- **Discussion method for choosing investigators:**
  - **-Experienced with diabetic gastroparesis**
  - **-Discussion of patient recruitment for gastroenterologists vs. diabetol gists**

***Final Decision:**

Review of Questions (attached) Carol Trapnell, All

General Topics for Discussion of Phase III Study:

- The nasal spray placebo may be different in taste so a placebo tablet was put in to help preserve the blind.

* Recommendation by experts:

- Length of trial: Three weeks was selected to avoid tolerance build-up plus it was within time periods used in previous trials with treatment.

* Recommendation by Experts:

- Suggested removal from second randomization of non-responders (<60% improvement) from McCallum. Discussion points- variability of symptoms, lack of validated assessment tool, and most non-responders will probably drop out of th study either before second randomization or at the time of second randomization on their own.

* Recommendation by experts:

- For last two visits of each randomization period, must the patients come into the clinic to complete the symptom questionnaires for two week in a row? Is the telephone acceptable for one of the questionnaires?

* Recommendation by experts:

Discussion on Symptomatic Questionnaire:

- Should there be a single question added to questionnaire on patient's "Global Feeling" of wellness?

* Recommendation by experts:

- Should there b guidelines to define th scores given for the symptomatic questi nnaire:

* Recommendation by experts:

- Discussion of whether a weekly diary would help to capture progress of patients; then one questionnaire only given at R2 for the last 24 hours or past week.

* Recommendation by experts:

- Discussion of the addition of a question that would identify a "Cardinal Symptom" and its progress during the study.

* Recommendation by experts:

- Discussion of a -3 to +3 scale or 1-4 for the questionnaire?

* Recommendation by experts:

- Discussion of need for definitions for the questionnaire questions for consistent interpretation.

* Recommendation by experts:

- Discussion of separate question to be added for "assess if you have any change in how your stomach feels since last visit scale that runs + to – over the last 4 weeks" only at weeks 4 and 8. For use as a secondary endpoint.

* Recommendation by experts:

- Discussion of Gastric Emptying: should it be d ne at baseline, R2 and End of Study. Method for gastric emptying needs standardization. Think about whether we want to stratify for gastric emptying.

* Recommendation by experts:

- Discussion of whether the patients need to be fasting when coming in? Need to be fasting for gastric emptying. Blood levels of drug to get population PK analysis do not need to be fasting.

* Recommendation by experts:

- Discussion of whether we want to get any prolactin levels.

* Recommendation of experts:

- Discussion of whether we want to do a test meal to see effect of test meal and gastric emptying on glucose levels.

* Recommendation of experts:

- Discussion of whether there should be a 1-2 week post study follow-up after end of Phase III study.

* Recommendation of experts:

Statistics:

- Discussion of whether a change of 3.5 points on the symptoms score of the questionnaire is clinically significant.

* Recommendation by experts:

- Discussion of what score should be used as the entrance criteria.

* Recommendation by xperts:

- **Should there be a weight given to certain symptoms?**

* **Recommendation by experts:**

Nasopharynx Questions:

- **Discussion of use of nasopharynx questionnaire or should investigator just ask for symptoms in general; do we want to be leading the patients and get more responses or leave open and probably get less positives. Irritation, bloody nose, and tenderness, or sores of the sinus or nasal passages were the most likely problem areas identified.**

* **Recommendation by experts:**

Medication Use Instruction Sheet:

- **Discussion of instructions to patient to include: missed meal dosing, how define meal, if missed dose but had a meal.**

* **Recommendation by experts:**

Gastric Emptying Study:

- **Discussion of procedures common to gastric emptying tests and specific for this study.**

* **Recommendation by experts:**

* **Recommendation by experts:**

- **Discussion of whether to include a 4 hour or 2 hour gastric emptying test (2 hour more standard) and what to feed as standard marked meal.**

* **Recommendation by experts:**

- **Discussion of how to recommend handling patients diabetic medications when fasting for the gastric emptying test.**

***Recommendation by experts:**

***Recommendation by experts:**

***Recommendation by experts:**

Inclusion Criteria:

- **Discussion of whether patients need an endoscopic exam of upper GI for inclusion into the study/rule out other causes for gastric distress or if accept previous diagnosis of gastroparesis.**

***Recommendation by experts:**

- **Discussion of whether it is necessary to do indepth documentation of autonomic neuropathy.**

***Recommendation by experts:**

- **Discussion of preferred washout period during baseline of any prokinetic medication.**

***Recommendation by experts:**

- **Discussion of labs to be collected and considered for inclusion.**

***Recommendation by experts:**

Exclusion Criteria:

- **Discussion of list of exclusions in protocol.**

***Recommendation by experts:**

- **Discussion of Excluded Medication.**

***Recommendation by experts:**

Concomitant List:

- **Discussion of list of conmeds.**

***Recommendation by experts:**

End of Study Visit:

- **Discussion of how much data can be reasonably collected at Premature Termination/Early Withdrawal Visit.**

***Recommendation by experts:**

Concomitant Meds during study:

- **Discussion of allowed medications during the randomized portion of the study.**

***Recommendation by experts:**

Procedure for unblinding Patient Treatment: Carol Trapnell is the SAE monitor. Investigators to discuss with her. Definition f SAEs per FDA guidelines and investigator discretion.

PK STUDY:

Expand length to 4 weeks to parallel Phase III study. PK measurements every two weeks.

There is currently little PK data available on metoclopramide. ½ life of the drug is 6 hours, current dosing recommendations we may be higher than needed to be effective. Could reduce side effects with lower available doses in nasal spray.

GENERAL INFORMATION:

Revisions in the protocols will be sent ASAP so well available for Investigators review prior t Investigators Meeting in

Possible protocols to pursue during open-label post study in selected sites include: post-meal hypoglycemia where will need symptoms plus glucose measurement; may use downloadable home glucose meters.

3:30 pm Conclusion of Discussion.

Minutes Prepared by:

Judith Chiostri _____